AF/1614
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CASE LD0268 NP

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Anastasia P. Winslow		July 19, 2004
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF Art Unit: 1614

FRANCIS Y.F. LEE

APPLICATION NO: 10/091,061

FILED: MARCH 5, 2002

FOR: COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES

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Enclosed herewith are three copies of the Appeal Brief in the above-identified application.

☒ Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $330 for payment of the appeal fee. An additional copy of this paper is here enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

☐ Enclosed is a Petition for Extension of Time.

Respectfully submitted,

Anastasia Winslow
Attorney for Applicant
Reg. No. 40,875

Bristol-Myers Squibb Company
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Date: July 19, 2004

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Anastasia P. Winslow		July 19, 2004
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

LEE

APPLICATION NO: 10/091,061

FILED: MARCH 5, 2002

Art Unit: 6706

Examiner: OSTRUP, CLINTON

FOR: **COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLIFERATIVE DISEASES**

APPEAL BRIEF ON BEHALF OF APPELLANT/APPLICANT

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REAL PARTY IN INTEREST

The real party in interest is Bristol-Myers Squibb Company (BMS). The inventor, Francis Lee, assigned his entire right, title, and interest in this application to BMS by assignment recorded at Reel No. 012680, Frame 0464, on March 5, 2002.

RELATED APPEALS AND INTERFERENCES

The applicant is not aware of any related appeals and interferences at this time.

STATUS OF CLAIMS

Applicant is appealing the rejection of claims 71, 72, 76-79, 90 and 98.

The final rejection mailed February 26, 2004, rejected all claims then pending, *i.e.* claims 1-8, 13-23, 26-28, 32-35, 71, 72, 74, and 76-100.

Claims 9-12, 24-25, 29-31, 36-70, 73, and 75 had been canceled by amendment filed November 12, 2003. These claims were canceled in view of a restriction requirement entered in an Office Action mailed April 24, 2003, and as redundant of other claims and/or directed to subject matter applicant elected to pursue in a divisional application.

Claims 1-8, 13-23, 26-28, 32-35, 74, 80-89, 91-97, and 99-100, are not being pursued in this appeal.

Subject matter of claims that are not the subject of this appeal, *i.e.*, canceled claims 9-12, 24-25, 29-31, 36-70, 73, and 75, as well as claims 1-8, 13-23, 26-28, 32-35, 74, 80-89, 91-97, and 99-100, is being pursued in a divisional application Serial No. 10/850,072, filed on May 20, 2004.

STATUS OF AMENDMENTS

On May 21, 2004, after the final rejection of all pending claims, applicant filed an amendment, canceling claims 1-100 and adding new claims 101-112.

New claims 101-112 were presented as encompassing the subject matter of the appealed claims, *i.e.*, 71, 72, 76-79, 90 and 98. This amendment was presented to place the appealed subject matter in better condition for consideration on appeal, as each of the appealed claims is a dependent claim. Thus, the new claims recite the appealed subject matter in independent format and enable the evaluation of this subject matter separately from other claims that are not the subject matter of the appeal. New claims recite use of 5-FU or capecitabine, as capecitabine enzymatically converts to 5-FU *in vivo*. *See* Amendment filed November 12, 2003, at p. 30. 5-FU was recited in previous claims. Thus, the new claims do not present any new subject matter, and they do not raise any issues other than whether the appealed claims should be allowed.

Nonetheless, in an Advisory Action mailed July 12, 2004, Examiner Shaojia Jiang, a new examiner on the case, advised that the new claims were not being entered on the ground that they raise new issues that would require further consideration and search.

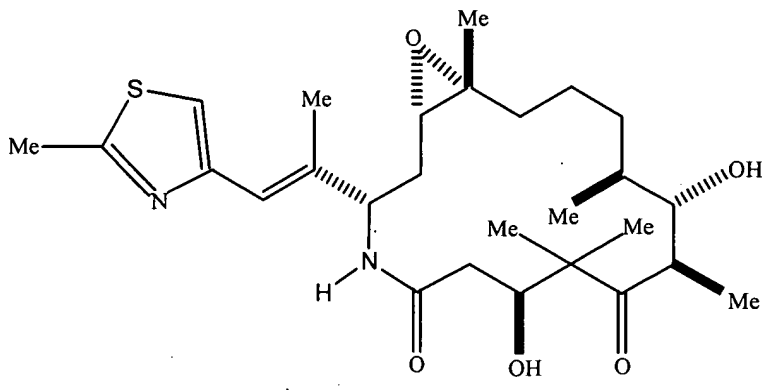
The appealed claims 71, 72, 76-79, 90 and 98, are included at Appendix A.

Claims 1, 2, 3, 4, 5, 6, 94, 96, and 97, on which appealed claims 71, 72, 76-79, 90 and 98 depend, are included at Appendix B.

New claims 101-112, the subject matter of the amendment after final rejection, are included at Appendix C.

SUMMARY OF INVENTION

The instant invention (recited in claim 71) is directed to a method of treating cancer by administering a synergistically-effective combination of the Compound (1), and the known anti-cancer agent capecitabine (otherwise known as Xeloda™). Compound (1) is [1S- 1R*,3R*(E),7R*,10S*, 11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione (which is otherwise known as "ixabepilone"), and has the following formula:



Another claimed aspect of the invention (recited in claims 72 and 76-77) comprises methods of administering the two agents, *i.e.*, capecitabine and Compound (1), in treatment protocols wherein capecitabine is administered after (claim 72), before (claim 76), and simultaneously with (claim 77), Compound (1).

Further aspects of the invention comprise methods of administering the two agents, *i.e.*, capecitabine and Compound (1), to treat cancerous solid tumors (claim 78), refractory tumors (claim 79), and cancers selected from bladder cancer, pancreatic cancer, prostate cancer, lung cancer, colorectal cancer, and breast cancer (claim 90).

Lastly, another aspect of the invention involved in this appeal comprises a pharmaceutical product having in a first package, capecitabine, and in a second package, Compound (1) (claim 98). This claim corresponds in scope with the method of treatment claim (claim 71) recited in terms of a product.

ISSUES

Whether a method for treating cancer with a novel, synergistic combination of two anti-cancer agents, namely, capecitabine and Compound (1), is properly rejected as *prima facie* obvious under Section 103, based on a prior art reference (more particularly, a one-page abstract of a Japanese article), generally discussing that additive *or* synergistic effects may be achieved by combining capecitabine with "taxanes" and/or a number of other compounds,

when a) other references teach against the combination of capecitabine and paclitaxel, b) there is no suggestion in the prior art that Compound (1) may be substituted for "taxanes" in the prior art combination to achieve the same or similar effects, and c) Compound (1) is not a taxane and there is no similarity in structure between Compound (1) and "taxanes"?

Whether a method for treating refractory tumors (*e.g.*, including tumors refractory or resistant to taxane treatment), with a novel, synergistic combination of two anti-cancer agents, namely, capecitabine and Compound (1), is properly rejected as *prima facie* obvious under Section 103, based on a prior art reference (more particularly, a one-page abstract of a Japanese article), generally discussing that additive *or* synergistic effects may be achieved by combining capecitabine with "taxanes" and/or a number of other compounds?

GROUPING OF CLAIMS

Claims 72, 76-79, 90, and 94 stand or fall together with claim 71.

Applicant submits that claim 79 is separately patentable. Claim 79 recites a method of treating refractory tumors (including tumors refractory to taxanes) with a synergistically-effective combination of Compound (1) and capecitabine. For example, the specification details at page 48, various cell lines that were used to test the claimed combinations, and among these were paclitaxel-sensitive and paclitaxel-resistant cell lines. (See spec. at 48, lines 19-31). As further illustrated at page 54, Tables 2 and 3, Compound (1) has different biological activity than paclitaxel with regard to these cell lines. However, the prior art relied upon by the Examiner to reject all of the appealed claims under Section 103 is a Japanese abstract (Saeki, *infra*), generally discussing that a combination of taxanes (which includes paclitaxel) and capecitabine may have additive or synergistic effects. Thus, the Examiner is substituting the use of taxanes in Saeki, with Compound (1) herein, to reject the claimed methods of treating *tumors refractory to taxanes*.

ARGUMENT -INTRODUCTION

No outstanding rejections remain under Sections 102 or 112. Accordingly, the requirements of 37 CFR 1.192, subparagraphs (i) through (iii) and (v) are inapplicable. Applicant will direct its arguments specifically to 37 CFR 1.192(iv).

The Examiner has rejected all claims on appeal under 35 USC § 103(a). The sole ground of rejection is that the claimed invention is obvious over (A) Vite *et al.*, WO 99/02514 (hereinafter "Vite"), in view of (B) Saeki *et al.*, Mechanism and Possible Biochemical Modulation of Capecitabine (Xeloda), a Newly Generated Oral Fluoropyrimidine (hereinafter "Saeki"). Vite and Saeki are the only references upon which the Examiner relies to reject all the claims.

Vite, which published on January 1999, corresponds to US Pat. No. 6,605,599, which issued on August 12, 2003, and is assigned to the present assignee. Compound 1 (ixabepilone) is Example 3 of Vite and the '599 patent and is recited in claim 8 therein. Thus, Vite is relied upon by the Examiner to establish that Compound (1) was prior art at the time the instant application was filed, which is not disputed.

Vite does not discuss specific combinations of Compound (1) with other named chemotherapeutic agents. Vite does not discuss or even identify any anti-metabolites, 5-FU, or capecitabine. Rather, the only reference to combinations in Vite is the following general comment:

> The compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula V can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different phase of the cell cycle, *e.g.*, S phase, than the present compounds of formula V, which exert their effects at the G_2-M phase.
>
> e.g. Thymidilate synthase inhibitors

DNA cross linking agents

Topoisomerase I and II Inhibitors

DNA Alkylating Agents

Ribonucleoside Reductase Inhibitors

Cytotoxic Factors e.g., TNF-alpha or

Growth factor inhibitors e.g., HER 2 receptor MAB's

[*See* page 10, lines 10-30 of Vite; Column 6, lines 18-31 of the '599 patent].

While Vite thus generally refers to combinations with other known anticancer agents that act in the S-phase, the potential combinations are indefinite. Seven classes of agents are identified – not including antimetabolites – and within these classes of agents, there are literally thousands of specific compounds, none of which is named in Vite. Potential combinations cannot be defined or enumerated. Additionally, there is no suggestion in Vite for combining Compound (1) with any one particular chemotherapeutic agent, no suggestion of synergy, and no suggestion of Compound (1) with any compound falling within the class of antimetabolites. Rather, Vite would lead one skilled in the field to combinations involving classes of agents other than antimetabolies, *i.e.*, thymidilate synthase inhibitors, DNA cross linking agents, topoisomerase I and II Inhibitors, DNA alkylating agents, ribonucleoside reductase inhibitors, cytotoxic factors e.g., TNF-alpha, and growth factor inhibitors, *e.g.*, HER 2 receptor MAB's.

The Examiner is relying on Saeki to support the 103 rejection. Saeki is a one-page English translation of an abstract of a Japanese article published in March 1999, announcing advantages of capecitabine (Xeloda™).

The pertinent section of Saeki is as follows:

> A new 5-FU analog, capecitabine, ... was generated to decrease the incidence of GI toxicity and to increase the efficacy. Capecitabine is designed as a prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is clinically used for gastric, breast and colorectal cancer patients undergoing single or combination chemotherapy in Japan ... In this

> regard, a high concentration of either 5'-DFUR or 5-FU in malignant tumors may be obtained by oral administration of capecitabine. In addition, *in vivo* study showed synergistic *or additive* effects of capecitabine combined with anti-cancer agents (*Taxanes, Mitomycin C or cyclophosphamide), cytokines, growth factors, and hormonal agents. ....*" (Emphasis supplied).

There is no discussion in Saeki as to whether synergistic effects were obtained with "taxanes"; there is no reference in Saeki as to which, *if any*, specific agents in the class of taxanes were tested and found to have advantageous activity with capecitabine; there is no suggestion whether combinations with taxanes were advantageous as compared with the other agents and classes of agents referred to in Saeki, *i.e.*, Mitomycin C or cyclophosphasmide, cytokines, growth factors, and hormonal agents; and there is no guidance as to which combinations with capecitabine are preferred and why.

As detailed below, applicant submits that the Examiner has engaged in a hindsight reconstruction of applicant's invention and has not made out a *prima facie* case of obviousness, rendering it unnecessary for applicant to come forward with affidavits or data. Among other reasons, the Examiner has, with the benefit of applicant's invention, selectively picked one reference to apply against the claimed invention, without considering the scope and content of the prior art in the field. Additionally, there is no suggestion or motivation in the prior art that Compound (1) may be selected from Vite, that the combination of taxanes and capecitabine may be selected from Saeki, and that Compound (1) may be substituted for the reference to "taxanes" in Saeki to achieve the claimed method of treating cancer with a synergistically-effective combination of two specific agents. The Examiner's selective modification of Saeki is based on knowledge obtained from applicant's disclosure and not based on any suggestion or motivation in the prior art. Applicant submits that the Examiner's reasoning here reflects exactly the type of hindsight reconstruction the *prima facie* case is designed to guard against.

POINT ONE

THE EXAMINER HAS NOT ENGAGED IN A PROPER OBVIOUSNESS INQUIRY AS THE SCOPE AND CONTENT OF THE PRIOR ART HAS NOT BEEN EVALUATED BUT INSTEAD, THE EXAMINER HAS ENGAGED IN A HINDSIGHT RECONSTRUCTION OF THE INVENTION WITH THE BENEFIT OF APPLICANT'S DISCLOSURE

The obviousness inquiry under *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 693 (1966), requires that the decision-maker consider: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the field at the time the invention was made, and (4) objective evidence of secondary considerations. *See also Para-Ordnance Mfg. v. SGS Importers Intern.*, 73 F.3d 1085, 1088, 37 USPQ2d 1237 (Fed. Cir. 1995).

Regarding the scope and content of the prior art, the combined teachings in a field need to be considered. Just as it is inappropriate to "pick and choose ... elements of assorted prior art references to recreate the claimed invention" (*Smithkline Diagnostic Inc. v. Helena Labs Corp.,* 859 F.2d 878, 887, 8 USPQ2d 1468 (Fed. Cir. 1988)), it is inappropriate for an Examiner to pick from a body of teachings one obscure reference as unequivocally establishing the state of knowledge in the field. Rather, "all teachings in the prior art must be considered to the extent they are in analogous arts," and "[w]here the teachings of two or more prior art references conflict, the Examiner must weigh the power of each reference ...." MPEP § 2143.01.

Here, these steps have been bypassed. The Examiner has picked Saeki as establishing the scope and content of the prior art, without considering conflicting prior art references. A proper obviousness analysis requires that the USPTO engage in a first step of determining the scope of prior art references in the field and what they teach, at the time of applicant's invention, including conflicting references.

For example, in Holmes, F., Seminars in Oncology, Vol. 23, No. 5 (October 1996) (hereinafter "Holmes"),[1] in discussing combinations including paclitaxel (a taxane compound), the author teaches against such combinations:

> First, an optimal dose and schedule for administration of paclitaxel has not yet been defined .... Second, empiric combinations of standard agents (e.g. cisplatin and doxorubicin) with paclitaxel have resulted in unexpected and/or severe toxicities related to sequence of administration and schedule. Third, *much of the initial in vitro and preclinical data were not supportive of synergistic combinations*, although more recent data do suggest that combinations *can be additive*. Finally, [hypothesis] ... suggests that a series of high doses of multiple *single* agents may be more effective in treating resistant cells and preventing the development of resistance than simultaneous use of the same agents at lower doses. [*Id.*] [emphasis supplied].

Then, in Johnson, K.R. *et al.*, "*5-Fluorouracil Interferes with Paclitaxel Cytotoxicity against Human Solid Tumor Cells*," Clinical Cancer Research, Vol. 3, Issue 10 (1997), at pp. 1739-45, the authors teach against the combination of 5-FU and paclitaxel:

> We found that 5-fluorouracil (5-FU), another antineoplastic agent that usually arrests tumor cells at the G1-S phase of the cell cycle, could significantly repress the cell-killing activity of paclitaxel in solid tumor cells, even when it was added simultaneously with paclitaxel. Further studies indicated that 5-FU actually inhibits the cytotoxic effects of paclitaxel on both mitotic arrest and apoptotic cell death, suggesting that 5-FU might interfere with paclitaxel cytotoxicity at an early stage ....Because recent clinical trials have used a combination of paclitaxel and 5-FU in the treatment of metastatic breast cancers, our results also suggest that the combination of these two drugs might not be as valuable in clinical chemotherapy.

Other references similarly teach against combinations of 5-FU (the prodrug to capecitabine), and paclitaxel, a taxane. For example, Johnson *et al.*, *"5-Fluorouracil Interferes with Taxol Cytotoxictyon Human Solid Tumor Cells,"* Proc. Am. Assoc. Cancer Res., Vol. 38, Meet. 88 (1997) *at* p. 323, reports that

[1] The Holmes's article and each of the articles and patent publications discussed herein were supplied to the USPTO via an IDS submitted on May 21, 2004.

"the 2 agents [5-FU and taxol] have a detrimental effect on each others action ....". An article to Kano *et al.*, "*5-Fluorouracil in Human Carcinoma Cell Lines in Vitro*," British Journal of Cancer, Vol. 74, Issue 5 (Sept. 1996), at pp. 704-10, reports that "simultaneous exposure to paclitaxel and 5-fluorouracil for 24 h showed mainly *sub*additive effects in A549, MCF7, and WiDr cell lines, whereas it showed *additive* effects in PA1 cells." (Emphasis supplied).

Other references teach against combinations involving 5-FU and other agents. For example, WO 01/49287 A1 to Sugen, at pages 41-42, reports that "the precise mode of action of fluorouracil is not clear," and "[w]hile use of the above combinations [involving 5-FU and various other agents, *e.g.*, methotrexate, leucovorin, interferon, platinum compounds, etc.] is increasing, none of them at present appear to provide a clear advantage over fluorouracil *alone* or fluorouracil in combination with leucovorin." (Emphasis supplied).

Considering the state of the art as a whole at the time of applicant's invention, it was not obvious that Compound (1) could be used together with capecitabine to obtain an advantageous combination having synergistic therapeutic activity. In rejecting the claims herein, the Office Action has not considered the state of the art and has not engaged in a proper obviousness inquiry. Rather, with the benefit of applicant's disclosure, a hindsight decision was made to selectively pick Saeki to "piece together" the invention and reject applicant's claims. For the foregoing reasons, a *prima facie* obviousness case has not been established, and it is respectfully requested that the Section 103(a) rejection be overturned.

POINT TWO

THE EXAMINER HAS NOT ESTABLISHED A *PRIMA FACIE* CASE OF OBVIOUSNESS AS THERE IS NO SUGGESTION OR MOTIVATION IN THE PRIOR ART TO MODIFY THE REFERENCES TO ARRIVE AT THE INSTANTLY-CLAIMED INVENTION

Against the backdrop of the *Graham* analysis (Point One, *supra*), the Federal Circuit has established three essential standards for the USPTO to meet, at a minimum, to establish a *prima facie* obviousness case. These standards have been erected to guard against the application of hindsight and inconsistent decisions. Specifically, a *prima facie* case of obviousness requires findings that: (1) the prior art contains *a suggestion or motivation* for modifying or combining the references; (2) the proposed modifications have a reasonable expectation of success in the prior art; and (3) the references teach or suggest *all* claim limitations. *See In re Chu*, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. *See also In re Gordon*, 733 F.2d 900, 221 USPQ2d 1125, 1127 (Fed. Cir. 1984) ("the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification").

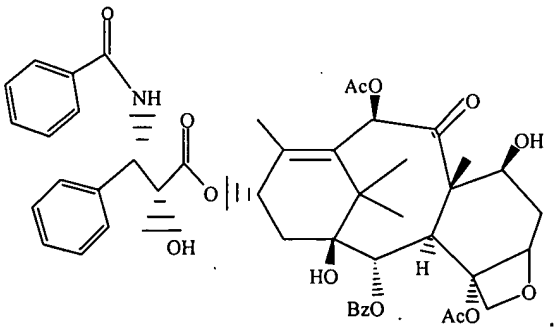
The burden of satisfying these requirements rests squarely with the USPTO in the first instance. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP § 2142. Accordingly, applicant is not required to come forward with data rebutting a *prima facie* case, unless and until the *prima facie* case is established.

Notably, in *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999), the court emphasized that it will demand a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art cases." *Id.* at 1617. This is necessary, the court explained, to guard against the "subtle but powerful attraction of a hindsight-based obviousness analysis." *Id.* Thus, under *In re Dembiczak*, for the Examiner to make an obviousness determination based on a

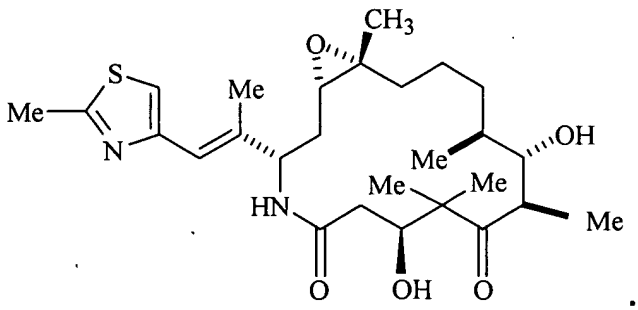
combination of references, the Examiner must make "particular findings" based on "actual evidence," and the "showing must be clear and particular." *Id.* at 1617.

Here, no particular findings based on actual evidence have been made. Instead, the Office Action argues that because capecitabine is reported to be effective to treat breast cancer, to have a high efficacy rate and low toxicity, it would have been obvious to make the instantly-claimed combination of capecitabine with Compound 1. This is not evidence or particularized findings, but a conclusory statement that is "entirely inadequate to support the rejection." *Id.* (*quoting In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977)). That references might be combined does not render the resultant combination obvious, unless there is a suggestion *in the prior art* for *making* the combination. MPEP § 2143.01. According to the Examiner's reasoning, any combination of capecitabine and any other agent would be obvious regardless of the state of the art or the compound's structure.

Here, there is no suggestion that use of "taxanes" as in Saeki can be substituted with Compound 1. It is not clear which, if any, taxane compounds were tested in Saeki to support the comment that synergistic *or* additive effects might be achieved. However, one of the taxanes is the well-known agent paclitaxel (a/k/a TAXOL®). Notably, Paclitaxel has the following formula (wherein Ac = acetyl),



In comparison, applicant's Compound (1) herein has the formula:



Thus, there is no similarity in these structures that would lead one skilled in the field to conclude that the compounds would have similar activities in combination therapies. The Examiner has acknowledged that this is an unpredictable field, and the unpredictability is heightened when dealing with combinations in view of, for example, drug-drug interactions and toxicity issues as identified in the references in Point One. Yet, remarkably, it appears that the Examiner has not even considered as relevant the fact that paclitaxel, one of the taxanes, has a vastly different structure from Compound (1).

Additionally, Compound (1) is effective in treating paclitaxel-resistant and paclitaxel-sensitive tumors (spec. at p. 21), demonstrating the compounds have different activity profiles. Pat-7 is specifically described as a TAXOL® (paclitaxel) resistant tumor type, against which the claimed combination is effective. Thus, there is no basis for an obviousness argument to the effect that there is a reasonable expectation of similar properties based on similarity in structures, and no scientific basis to substitute Compound (1) for the reference to "taxanes" in Saeki. *Cf.* MPEP § 2144.09. Paclitaxel and Compound (1) are different compounds, with different structures and different activities.

For the foregoing reasons, applicant submits a *prima facie* obviousness case has not been established and requests that the rejection of the claims be overturned.

POINT THREE

THE EXAMINER HAS NOT ESTABLISHED A *PRIMA FACIE* CASE OF OBVIOUSNESS AS THERE IS NO REASONABLE EXPECTATION OF SUCCESS IN THE PRIOR ART AND ALL CLAIM LIMITATIONS HAVE NOT BEEN MET

The *prima facie* test established by the Federal Circuit also requires that the USPTO Examiner demonstrate that the proposed modifications have a reasonable expectation of success in the prior art, and that the references teach or suggest *all* claim limitations. *See In re Chu*, *supra*, 36 USPQ2d at 1094. The reasonable expectation of success must be found in the prior art, not in applicant's disclosure. *In re Dow Chem.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("Both the suggestion and the expectation of success must be founded in the prior art").

Here, there was no reasonable expectation of success in the prior art that Compound (1) could be combined with capecitabine to achieve a synergistically effective combination of agents. Saeki does not support a reasonable expectation of success for this combination, because, *inter alia*, Saeki does not state whether synergistic, as opposed to additive, effects were achieved with capecitabine and taxanes, or which if any taxane compound was examined therein. Saeki provides no guidance as to why the combinations involving capecitabine and taxanes, M\tomycin C, or cyclophosphasmide, cytokines, growth factors, and/or hormonal agents, were selected for discussion, which if any of these were preferred and why, and what if any guiding factors might be considered by one skilled in the field in developing further combinations not mentioned therein.

Beyond this, as to claim 79, there is no reasonable expectation of success and all claim limitations have not been met. This claim is specifically directed to a method of treating refractory tumors including tumors refractory to paclitaxel which is supported in the specification. Considering that Saeki involves combinations of taxanes (including paclitaxel) and capecitabine, Saeki provides no reasonable expectation that a combination therapy could be obtained to treat

refractory tumors, including tumors refractory to paclitaxel, and this claim limitation is not met. Thus, the obviousness rejection should be overturned.

CONCLUSION

For the foregoing reasons, applicant submits that the USPTO Examiner has not presented a *prima facie* obviousness case with respect to applicant's claims 71, 72, 76-79, 90 and 98. Applicant requests that the rejection be overturned and that this application proceed to issuance with regard to claims 71, 72, 76-79, 90 and 98.

Respectfully submitted:

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Dated: July 19, 2004

APPENDIX A

(Appealed claims 71, 72, 76-79, 90 and 98)

71. The method of Claim 1 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-neoplastic cytotoxic agent is capecitabine.

72. The method of Claim 2 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-neoplastic cytotoxic agent is capecitabine.

76. The method according to Claim 3 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-neoplastic cytotoxic agent is capecitabine.

77. The method according to Claim 4 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-

oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-neoplastic cytotoxic agent is capecitabine.

78. The method according to Claim 5 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-neoplastic cytotoxic agent is capecitabine.

79. The method according to Claim 6 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione and the anti-neoplastic cytotoxic agent is capecitabine.

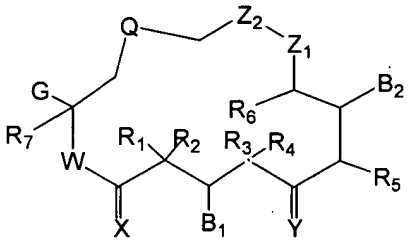
90. The method according to Claim 71, comprising the treatment of a cancer selected from at least one of bladder cancer, pancreatic cancer, prostate cancer, lung cancer, colorectal cancer, and breast cancer.

98. The product according to Claim 97, wherein the cytotoxic agent is at least capecitabine.

APPENDIX B

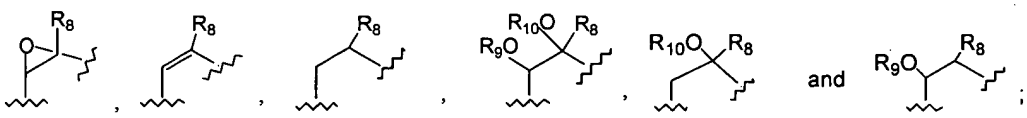
(Claims 1, 2, 3, 4, 5, 6, 94, 96, and 97,
on which appealed claims 71, 72, 76-79, 90 and 98 depend)

1. A method for the treatment of cancer, which comprises administering to a mammal in need of treatment therefor a synergistically, therapeutically effective amount of (1) at least one anti-neoplastic cytotoxic agent, and (2) at least one compound of formula I,

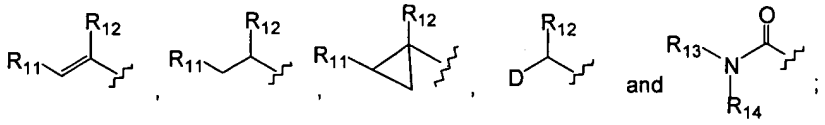


wherein:

Q is selected from the group consisting of



G is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo,



W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16} ; OR_{17}, OR_{17}; NOR_{18}; H, $NHOR_{19}$; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein when Y is OR_{17}, OR_{17} , two R_{17} can be joined so that Y is a cyclic ketal;

Z_1 and Z_2 are independently selected from the group consisting of CH_2, O, NR_{23}, S, and SO_2, wherein only one of Z_1 and Z_2 can be a heteroatom;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$;

D is selected from the group consisting of $NR_{28}R_{29}$, $NR_{30}COR_{31}$ and saturated heterocycle;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are independently selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl, R_1 and R_2 can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl, R_3 and R_4 can be joined to form a cycloalkyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are independently selected from the group consisting of H, alkyl, and substituted alkyl, or where Y is OR_{17}, OR_{17}, two R_{17} can be a joined to form a cyclic ketal;

R_8, R_{11}, R_{12}, R_{28}, and R_{30} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo;

R_{15}, R_{23} and R_{29} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo, $R_{32}C=O$, $R_{33}SO_2$, hydroxy, O-alkyl or O-substituted alkyl;

R_{32}, and R_{33} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo; and pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and stereoisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

Z_1 and Z_2 are CH_2; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above,

are excluded.

2. The method according to Claim 1 wherein the anti-neoplastic cytotoxic agent is administered following administration of the compound of formula I.

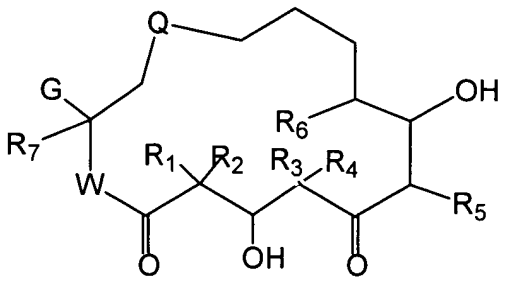
3. The method according to Claim 1, wherein the anti-neoplastic cytotoxic agent is administered prior to the administration of the compound of formula I.

4. The method according to Claim 1 wherein the anti-neoplastic cytotoxic agent is administered simultaneously with the compound of formula I.

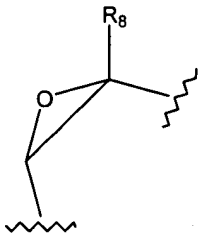
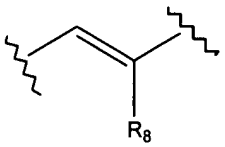
5. The method according to Claim 1 comprising the treatment of cancerous solid tumors.

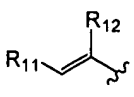
6. The method according to Claim 1 comprising the treatment of refractory tumors.

94. A pharmaceutical product for administering a combination of anti-proliferative agents to a mammal, the product comprising in a first package, a cytotoxic agent selected from at least one of an anti-metabolite and an alkylating agent, and in a second package, a compound having the formula,



wherein:

Q is  or  ;

G is  ;

W is O or NR_{15};

R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are independently selected from the group consisting of H, alkyl, substituted alkyl, and aryl;

R_8, R_{11}, and R_{12} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl and heterocyclo; and

R_{15} is H, alkyl, or substituted alkyl.

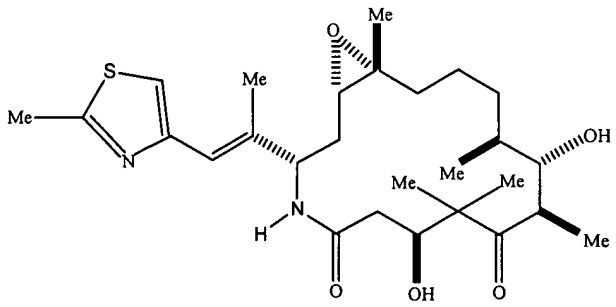
96. The product according to Claim 94 wherein the compound of formula I is [1S-1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

97. The product according to Claim 96 wherein the cytotoxic agent is an anti-metabolite selected from the group consisting of Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Gemcitabine, Capecitabine, and/or mixtures thereof.

APPENDIX C

(New claims 101-112, the subject matter of the amendment after final rejection, designed to place the appealed subject matter in better condition for appeal)

101. A method for treating cancer which comprises administering to a mammal a therapeutically-effective combination of chemotherapeutic agents comprising (1) at least one anti-metabolite selected from capecitabine and/or 5-fluorouracil, and (2) Compound (1), having the formula,



102. The method according to claim 101, wherein the anti-metabolite is capecitabine administered following the administration of Compound 1.

103. The method according to claim 101, wherein the anti-metabolite is capecitabine administered before the administration of Compound 1.

104. The method according to claim 101, wherein the anti-metabolite is capecitabine administered substantially simultaneously with the administration of Compound 1.

105. The method according to claim 101, comprising the treatment of cancerous solid tumors.

106. The method according to claim 101, comprising the treatment of refractory tumors.

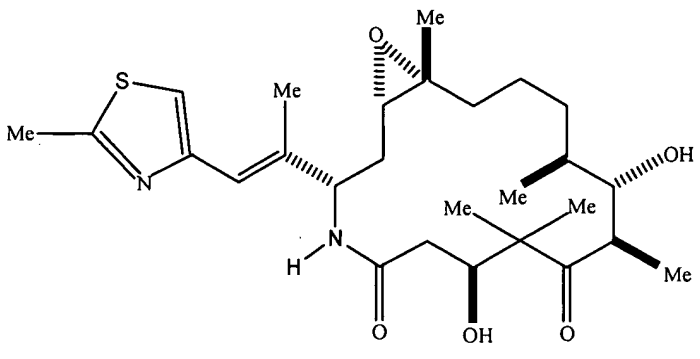
107. The method according to claim 101, wherein the cancer is metastatic breast cancer.

108. The method according to claim 101, wherein the cancer is lung cancer.

109. The method according to claim 101, wherein the cancer is prostate cancer.

110. The method according to claim 101, wherein the cancer is pancreatic cancer.

111 . A pharmaceutical product for administering a combination of anti-proliferative agents to a mammal, the product comprising in a first package an anti-metabolite selected from capecitabine and/or 5-fluorouracil, and in a second package, Compound (1), which is,



112 . The product according to Claim 111 wherein the anti-metabolite is capecitabine.